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PHOTOCYCLOADDITIONS TO 3-PHENYL-1,2-BENZISOTHIAZOLE

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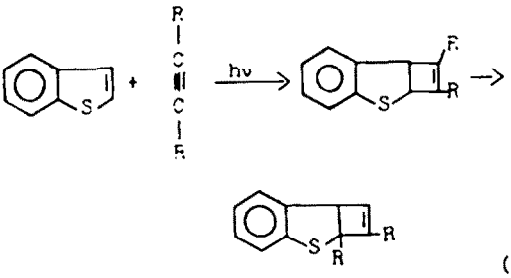
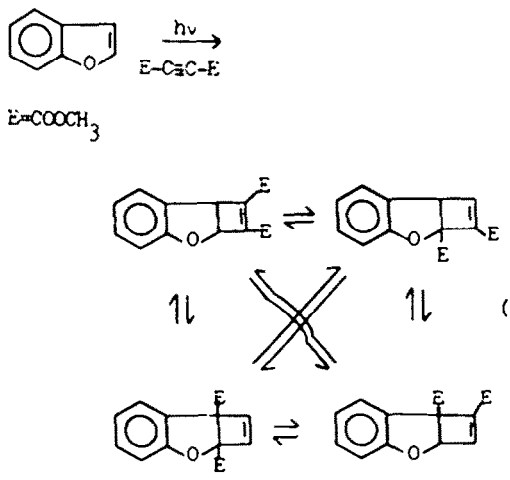
Abstract—Photocycloaddition reactions of 3-phenyl-1,2-benzisothiazole to alkenes yield derivatives of 2,3-dihydro-1,4-benzothiazepine in one step reactions. The photoadditions are both regio and stereospecific.

Photocycloaddition reactions of fused heterocycles have been of interest for many years.[1-6] Thus we have reported that [2+2]π photoprocesses of benzo(b)thiophene and alkynes give both unrearranged and rearranged adducts (I), the latter arising from the former by direct excitation through a charge transfer band of the unrearranged adduct.[1,2,6] We have also reported that the products from benzo(b)furans and alkynes derive from more extensive and deep seated rearrangements,[4] (2).

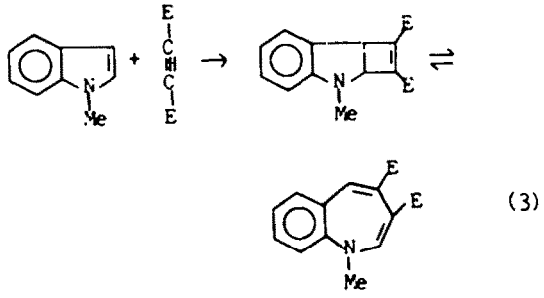


(1)



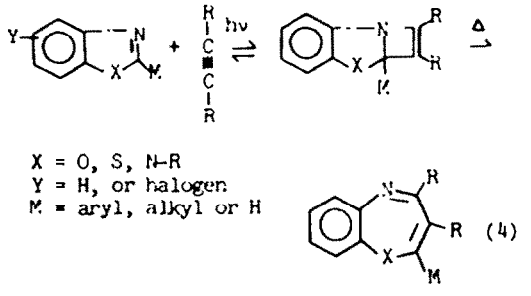
(2)

Indoles and alkynes give adducts which do not rearrange photochemically, but which rearrange thermally to benzazepines and under mild conditions[3,7], (3).



(3)

Based on these observations it occurred to us that photocycloadditive reactions of heterocyclic precursors such as benzimidazole, benzoxazole and benzothiazole (or their atomic isomers), might provide direct synthetic entry to the pharmacologically active benzodiazepines and potentially active analogs in the benzoxazepine and benzothiazepine[11] series (4). Recent studies[9,10] have been directed toward this goal, with some specific success[12]. Herein we report photocycloadditions of benzisothiazole and its derivatives.

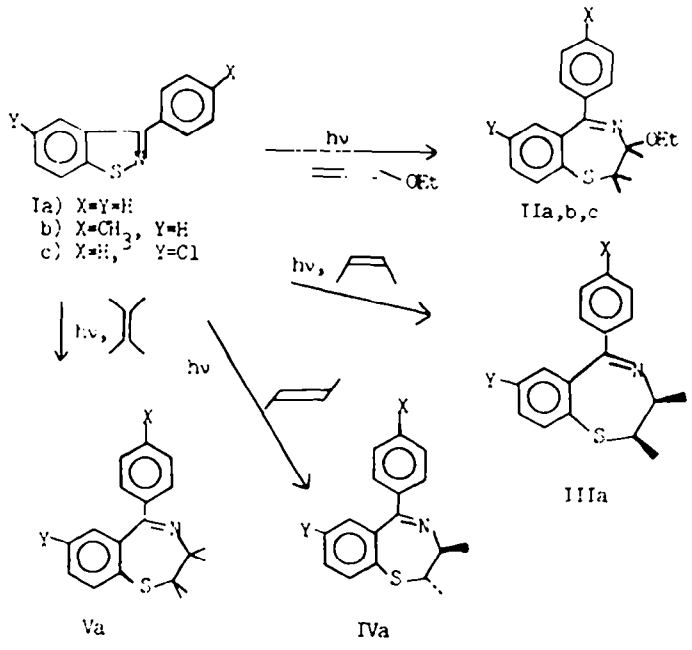


X = O, S, N-R
Y = H, or halogen
M = aryl, alkyl or H

(4)

RESULTS

3-Phenyl-1,2-benzisothiazole (I), when irradiated in the presence of alkenes gave 2,3-dihydro-1,4-benzothiazepines (II, III, IV and V) in good yield (70–86%). The irradiation was performed in Pyrex tubes with a 450 W, medium-pressure mercury lamp at *ca.* 15°C or in Rayonet reactor at 300 nm after the reaction mixture had been purged with nitrogen or degassed using several freeze-thaw cycles.



Scheme 1.

I with ethyl vinyl ether gave only one photoproduct. That this product was not a thermal product was indicated since no benzothiazepine was formed when I and ethyl vinyl ether were allowed to stand in the dark under the same conditions as was the mixture irradiated. Even two days reflux in ethyl vinyl ether gave no detectable amount of the cycloadduct later identified as II.

Structures of the photoproducts were determined by spectroscopic and chemical evidence and the structure of adduct IIa was confirmed by X-ray analysis.

The ^{1}H NMR spectrum of the photoadduct II is characterized by a one proton doublet of doublets (on C-3) centered at δ 4.50; a four proton multiplet at δ 3.20–4.05 (two protons on C-2 and $-CH_2-$ of Et group) and a three proton triplet at δ 1.24 ($-CH_3$ of Et group). The doublet of doublets at δ 4.50 has both a small coupling constant (J = 4.8 Hz) and a large one (J = 10.4 Hz) resulting from coupling with *cis*- and *trans*-protons on C-2, respectively. This is in good agreement with the vicinal coupling constant of cycloadduct III (J = 4 Hz), III being obtained from photoreaction with *cis*-2-butene, as well as with the vicinal coupling constant of cycloadduct IV (J = 10.5 Hz), obtained from reaction I with *trans*-2-butene. We can generalize that in 2,3-dihydro-1,4-benzothiazepines the *cis*-vicinal coupling constant is 4–5 Hz and *trans*-vicinal coupling 10–11 Hz. The regiospecific formation of 2,3 - dihydro - 3 - ethoxy - 5 - phenyl - 1,4 - benzothiazepine from ethyl vinyl ether

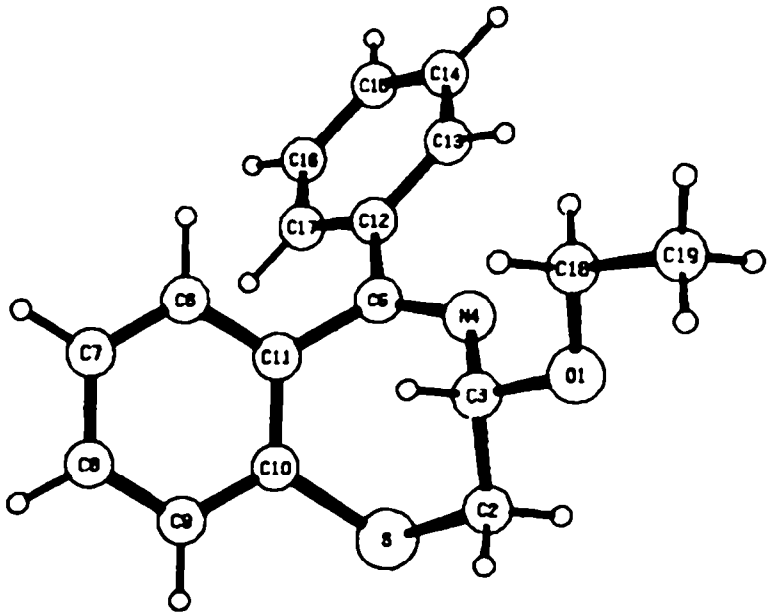


Fig. 1. X-ray crystal structure of 2,3-dihydro-3-ethoxy-5-phenyl-1,4-benzothiazepine (IIa).

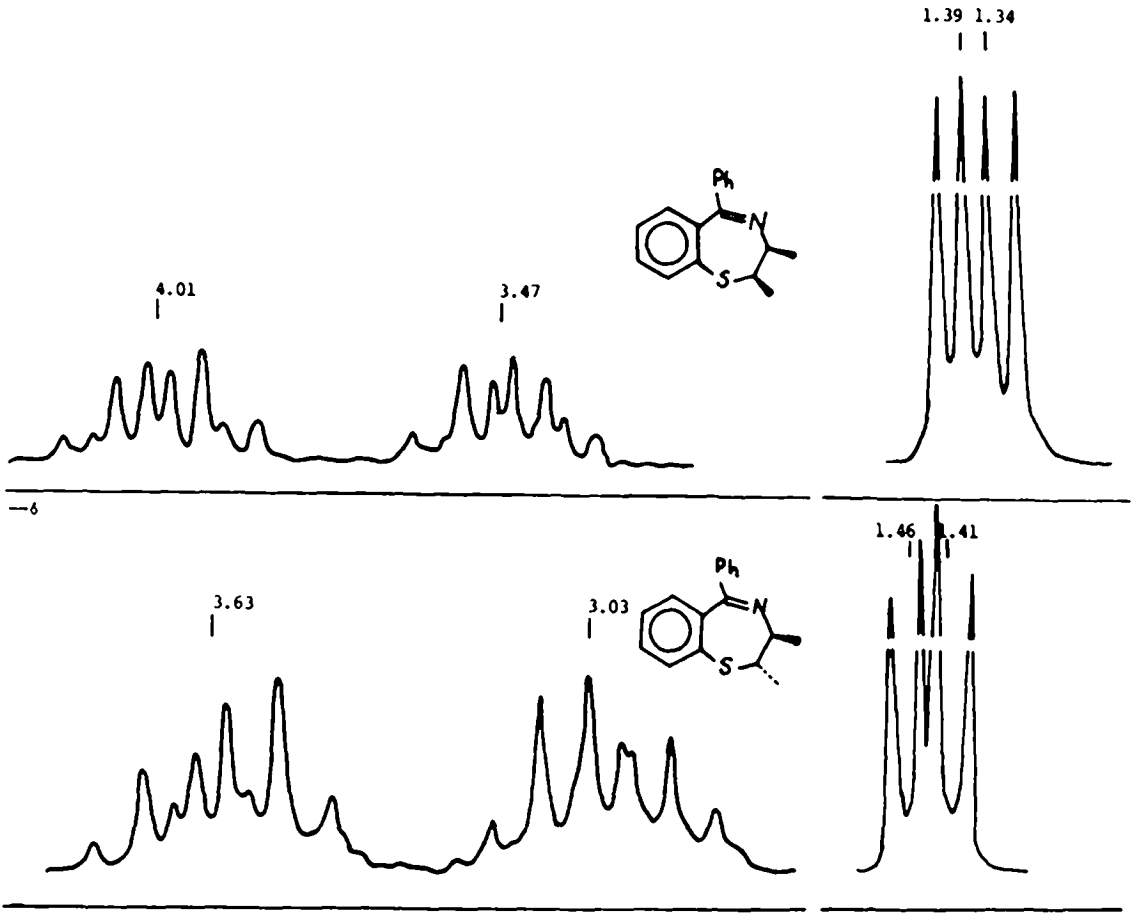


Fig. 2. The ^{1}H NMR spectrum of 2,3-dihydro-2,3-dimethyl-5-phenyl-1,4-benzothiazepines III and IV in $CDCl_3$.

and 3-phenylbenzisothiazole was confirmed by X-ray analysis, the pattern being shown in Fig. 1.

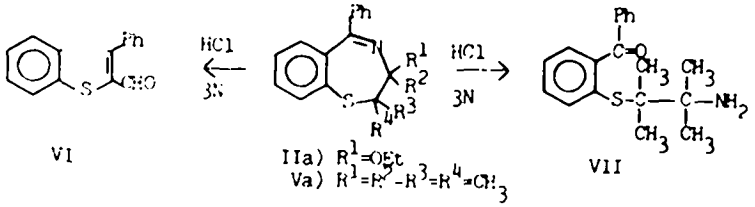
Cyclic adduct IIIa, the only product isolated from the photoreaction of 3-phenyl-1,2-benzisotheazole (I) and *cis*-2-butene, has, in the NMR spectrum, two well resolved doublets of quartets centered at δ 4.01 and 3.47, assigned to two ring protons. The same ring protons in *trans*-configuration in cycloadduct IVa are shifted upfield to δ 3.63 and 3.03. (The partial NMR spectra of IIIa and IVa are given in Fig. 2.)

The NMR spectrum of the adduct Va looks very simple; beside the 9 aromatic proton multiplet between δ 6.98 and 7.64 there are two singlets at δ 1.48 and 1.11.

The photocycloadducts are stable toward hydrochloric acid solution at ambient temperature. Treating them with gaseous HCl in carbon tetrachloride converts them to the corresponding hydrochloride salts.

Hydrolysis of the cycloadduct Va, carried out by refluxing it in 3N HCl for 3 days however, and extracting it from the basic solution gave VII, (5). The structure of product VII was established from spectroscopic data. This material showed, in addition to an NH_2 absorption in the IR (3370 and 3310 cm^{-1}), a CO absorption at 1670 cm^{-1}. Photoadduct IIa hydrolyzes much faster than IIIa or Va showing the correct assignment of the structure and the presence of the easily hydrolysed $-\overset{|}{C}=N-\overset{|}{C}-$ OEt group. Thus, treating IIa with 3N hydrochloric acid at elevated temperature (~50°) resulted in the ring opening and formation of the product which showed in the NMR spectrum only aromatic pattern and a singlet at δ 9.93. The characteristic CH stretching frequency at 1670 cm^{-1}, as well as the *m/e* $[M-1]^+$ in the mass spectrum suggested formation of 3-phenylbenzo(b)thiophene-2-carboxaldehyde (VI).

In the IR spectrum 2,3-dihydro-1,4-benzothiazepines show strong absorption between 1610–1625 cm^{-1} and this is assigned as the carbon-nitrogen double bond stretching frequency.



(5)

2,3-Dihydro-1,4-benzothiazepines show a very weak molecular ion and the base peak corresponds to the mass of the starting 3-phenyl-1,2-benzisothiazoles in the mass spectrum.

DISCUSSION

The photoaddition of alkenes to 3 - phenyl - 1,2 - benzisothiazole is formally $_{\pi}2 + _{\pi}2$ addition. As we have seen from the described results it is regiospecific with respect to the direction of the addition of the ethyl vinyl ether and stereospecific with respect to the reaction with *cis*- and *trans*-2-butene. The reaction appears not to be a triplet reaction since it is not sensitized by either benzophenone (E_T = 69 kcal/mole) or thioxanthone (E_T = 59 kcal/mole). The triplet energy of 3-phenyl-1,2-benzisothiazole, measured from its phosphorescence spectrum in frozen ethanol glass, was found to be 55 kcal/mole.

A series of several mechanisms are possible to explain these results. Both charge transfer and radical intermediates are conceivable. These several alternatives are outlined in Scheme 2.

One might rationalize that the reaction proceeds via homolytic cleavage of the S–N bond and formation of the biradical VIII. This appeared to be a most logical mechanism in view of the reported photo ring opening of 1,2-benzoisothiazole[13] to 2-cyanothiophenol as well as the formation, from 1,2-benzisothiazole and dimethyl acetylenedicarboxylate, of linear adducts.[9] The 1,4-biradical VIII, though it could explain the formation of adduct II, does not account for the stereospecific formation of adducts III and IV since it would have to be assumed that reaction of VIII with *cis*- and *trans*-2-butene be concerted.

The same argument pertains if an adduct biradical, such as IX[14], is the intermediate. Unless IX undergoes ring closure at a rate significantly faster than rotation about the $-CHCH_3-CHCH_3$ bond, products would not be formed stereospecifically.

Other possibilities include a concerted $[2+2]\pi$ cycloaddition to the S–N bond, producing adduct X. If adduct X was produced stereospecifically, and ring opened stereospecifically, the observed products would be explained.

Additional information about the mechanism of the photocycloaddition is obtained by investigating the reaction in different solvents. The formation of the photocycloadduct IIa is solvent dependent (Fig. 3). When the irradiation of 3-phenyl-1,2-benzisothiazole (I) and ethyl vinyl ether was carried out in different solvents under comparable conditions the efficiency of adduct formation is increased in the more polar solvent, acetonitrile. This rules out concerted cycloadditions since no charge separation would derive in these reactions in approaching the transition state.

Among the olefins 2,3-dimethyl-2-butene, *cis*-2-butene and *trans*-2-butene, the photoadducts are formed much faster from the hindered olefin 2,3-dimethyl-2-butene than from either of the less hindered ones *cis*-2-butene or *trans*-2-butene. In view of the fact that 2,3-dimethyl-2-butene has a substantially lower ionization potential than either *cis* or *trans*-2-butene,[15] this implies that ionization of the olefin occurs prior to the rate limiting step. Coupled with the observed acceleration in polar-as contrasted to non-polar-solvents still another mechanism is suggested that being first formation of a solvent sensitive exciplex[16] which may dissociate to a radical cation/anion pair. This mechanism is outlined in Scheme 3. As is the

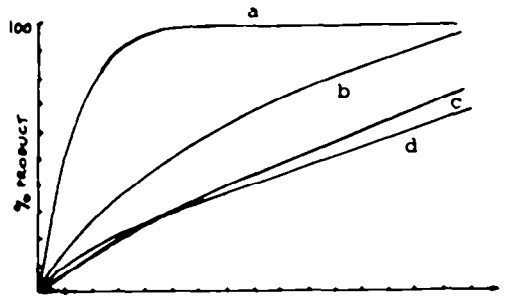
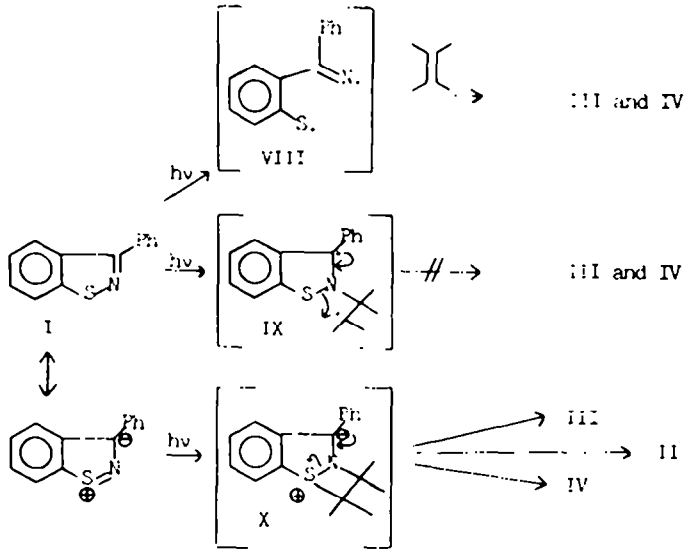
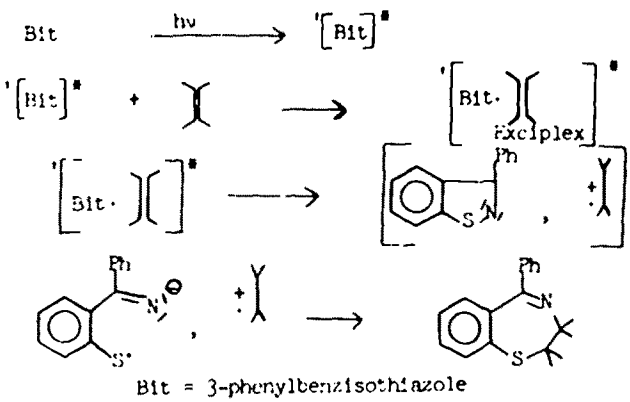


Fig. 3. Formation of the photocycloadduct IIa in different solvents: (a) ethyl vinyl ether, (b) acetonitrile, (c) benzene, (d) hexane.



Scheme 2.



Scheme 3.

case with biradical intermediates, ring closure of the radical cation/radical anion must be more rapid than C–C isomerizations. These mechanistic features are still under investigation.

EXPERIMENTAL

General. ^{1}H NMR spectra were recorded on Varian CFT-20 spectrometer. Unless otherwise indicated, $CDCl_3$ is used as the solvent with TMS as the internal standard. Coupling constants (J) are in Hertz, and chemical shifts are in δ values IR spectra were obtained on a Perkin-Elmer 337 spectrophotometer, UV spectra from a Beckman Acta IV spectrophotometer or with a Varian/Cary 219 spectrophotometer. Fluorescence and phosphorescence spectra were recorded on a Perkin Elmer MPF-44 a fluorescence spectrophotometer.

Ethyl vinyl ether and 2,3-dimethyl-2-butene were purchased from Aldrich Chemical Company. *cis-* and *trans-*2-Butene were obtained from Matheson.

3-Phenyl-1,2-benzisothiazole (Ia) was prepared as described[17,18]: m.p. 69–70 (lit.[17] 71–2°). *3-Tolyl-1,2-benzisothiazole* (Ib) was prepared following the procedure for 3-phenyl-1,2-benzisothiazole[17] and characterized by spectroscopic data: m.p. 51–2°: ^{1}H NMR ($CDCl_3$) 2.45 (s, 3, CH_3), 7.2–8.3 (m, 8, aromatic); UV (λ max, ϵ, 95% EtOH) 233 (16250), 245 (12750, Sh), 312 (10125); mass spectrum, *m/e* 225 (M^+).

5 - Chloro - 3 - phenyl - 1,2 - benzisothiazole (Ic), was prepared from 3 - phenyl - 5 - amino - 1,2 - benzisothiazole[18] via a Sandmeyer reaction[19]: m.p. 98–9°; ^{1}H NMR (δ, $CDCl_3$) 7.3–8.2 (m, aromatic); UV (λ max, ϵ, 95% EtOH) 238 (12390), 266 (3940, Sh), 317 (5530), 322 (5430); mass spectrum, *m/e* 245 (M^+).

Irradiation of Ia, Ib *and* Ic *in the presence of ethyl vinyl ether.* Approximately 0.02 M of a soln of the 1,2-benzisothiazoles (Ia, b, c) in the ethyl vinyl ether was purged with N_2 and irradiated in Pyrex glass tube in a Rayonet reactor at 300 nm for 90–150 hr. After evaporation of the ethyl vinyl ether the remaining photomixture was chromatographed on a silica gel column with hexanes/ether as the eluent. The photoproducts were isolated after separation of the unreacted starting material by changing the ratio of the solvents. The yield of isolated products was, in all cases, between 70 and 80%.

2,3 - Dihydro - 3 - ethoxy - 5 - phenyl - 1, 4 - benzothiazepine (IIa). Yield 80% (90 hr irradiation); m.p. 134–5°; ^{1}H NMR (δ, $CDCl_3$) 7.06–7.73 (m, 9H), 4.50 (dd, 1H, J = 4.8 and 10.4 Hz), 3.20–4.05 (m, 4H), 1.24 (t, 3H, J = 7.0); UV (λ max, ϵ, 95% EtOH), 252 (15660), 300 (1380); mass spectrum *m/e* 283 (M^+, 13%), 254 (30), 238 (6), 226 (23), 211 (base peak). (Found: C, 72.18; H, 6.02; N, 4.94; S, 11.33. Calc. for $C_{17}H_{17}NSO$: C, 72.05; H, 6.05; N, 4.94; S, 11.32%).

2,3 - Dihydro - 3 - ethoxy - 5 - tolyl - 1,4 - benzothiazepine (IIb) Yield 74% (138 hr of irradiation); m.p. 94.5–95°; ^{1}H NMR (δ, $CDCl_3$) 7.06–7.70 (m, 8H, aromatic), 4.48 (dd, 1H, J = 4.8 and 10.4 Hz), 3.19–4.03 (m, 4H), 2.38 (s, 3H, CH_3), 1.23 (t, J = Hz); UV (λ max, ϵ, 95% EtOH) 236 (11890), 253 (15500), 260 (14700, Sh) 310 (1240); mass spectrum *m/e* 297 (M^+), 268, 240, 225 (base peak). (Found: C, 72.50; H, 6.40, N, 4.72; S, 10.78. Calc. for $C_{18}H_{19}NSO$: C, 72.69; H, 6.44; N, 4.71; S, 10.76%.)

7 - Chloro - 2,3 - dihydro - 3 - ethoxy - 5 - phenyl - 1,4 - benzothiazepine (IIc). Yield 70% (146 hr irradiation); m.p. 126.5–127°; ^{1}H NMR (δ, $CDCl_3$) 7.11–7.72 (m, 8H, aromatic), 4.47 (dd, 1H, J = 4.8 and 10.4 Hz), 3.20–4.04 (m, 4H); 1.25 (t, 3H, CH_3, J = 7.0 Hz); UV (λ max, ϵ, 95% EtOH) 239 (15300), 256 (18200) 310 (1270); mass spectrum *m/e* 317 (M^+, 12%) 288 (37), 260 (28), 245 (base peak), 210 (49). (Found: C, 64.37; H, 4.95; N, 4.41; S, 10.21. Calc. for $C_{17}H_{16}ClNOS$: C, 64.24; H, 5.08; N, 4.41; S, 10.09%.)

Irradiation of 3-phenyl-1,2-benzisothiazole (Ia) *in the presence of cis-2-butene.* A soln of Ia (0.04 m) in liquid *cis*-2-butene was degassed by several freeze thaw cycles and irradiated in a sealed Pyrex tube at *ca.* 10° with a medium pressure mercury lamp for 110 hr. Upon opening the tube *cis*-2-butene evaporated and the residue was chromatographed on a silica gel column using hexane/ether as the eluent. Compound IIIa, (78%) was isolated as a colorless oil; ^{1}H NMR (δ, $CDCl_3$) 7.04–7.67 (m, 9, aromatic), 4.01 (dq, 1H, J = 6.7 and 4.0 Hz), 3.47 (dq, 1H, J = 6.5 and 4 Hz). 1.39 (d, 3H, CH_3, J = 6.5 Hz), 1.34 (d, 3H, CH_3, J = 6.7 Hz); mass spectrum *m/e* 267 (M^+, 12%), 211 (base peak): IR (neat) 1610 cm^{-1} (C=N; UV (λ max, ϵ, 95% EtOH) 230 (15480), 252 (14420), 302 (1070).

Irradiation of 3-phenyl-1,2-benzisothiazole (Ia) *in* trans-2-*butene.* Ia (232.5 mg; 1.1 m mol) was dissolved in 2 ml benzene and 15 ml *trans*-2-butene was added. The soln was degassed by several freeze thaw cycles and irradiated in a sealed Pyrex tube in Rayonet at 300 nm for 136 hr. After allowing the *trans*-2-butene to evaporate the mixture was purified on TLC plates diluting with hexane/ether mixture. Obtained was only 8% of IVa; m.p. 86–7°; ^{1}H NMR (δ, $CDCl_3$) 7.09–7.71 (m, 9H, aromatic), 3.63 (dq, 1H, J = 6.5 and 10.5 Hz), 3.03 (dq, 1H, J = 6.0 and 10.5 Hz) 1.46 (d, 3H, CH_3, J = 6Hz), 1.41 (d, 3, CH_3, J = 6.5 Hz); mass spectrum *m/e* 267 (M^+, 5), 211 (base peak); UV (λ max, ϵ, 95% EtOH) 212 (20890), 230 (16880), 249 (15710), 306 (940). (Found: C, 76.26; H, 6.31; N, 5.14; S, 11.88. Calc. for $C_{17}H_{17}NS$: C, 76.36; H, 6.41; N, 5.24; S, 11.99%.)

Irradiation of 5 - chloro - 3 - phenyl - 1,2 - benzisothiazole (Ic) *in the presence of* cis- *and* trans-2- *butene.* Ic (120 mg; 0.49 m mol) dissolved in 25 ml liquid *cis*-butene, degassed by several freeze thaw cycles and irradiated with medium pressure mercury lamp in a sealed Pyrex tube at about 10° for 140 hr. The tube was opened and *cis*-2-butene allowed to evaporate. The residue was chromatographed on silica gel column with hexane/ether as the eluent. Isolated was 129.8 mg (88%) of IIIc, m.p. 93–4°; ^{1}H NMR (δ, $CDCl_3$) 7.08–7.66 (m, 9H, aromatic), 3.97 dq, 1H, J = 6.7 and 4.2 Hz), 3.43 (dq, 1H, J = 6.3 and 4.2 Hz), 1.39 (d, 3, CH_3, J = 6.3 HZ), 1.33 (d, 3, CH_3, J = 6.7 Hz); mass spectrum *m/e* 301 (M^+, 3%), 259 (33), 249 (base peak); UV (λ max, ϵ, 95% EtOH) 212 (41540), 232 (21670), 254 (17460), 282 (5120), 310 (1500).

The experiment with *trans*-2-butene was carried out with the same quantities and conditions of irradiation. Only 33% of IVc was found by GC analysis though it was not isolated. In the NMR spectrum, the product IVc (in the mixture with the starting material) shows the following characteristic signals (δ, $CDCl_3$): 3.57 (dq, 1H, J = 6.7 and 10.75 Hz), 2.93 (dq, 1H, J = 6.0 and 10.75 Hz), 1.42 (d, 3H, CH_3 J = 6.0 Hz), 1.38 (d, 3, CH_3, J = 6.7 Hz).

Irradiation of 3-phenyl-1,2-benzisothiazole (Ia) *in the presence of 2,3-dimethyl-2-butene.* To 344 mg (1.63 m mol) of Ia, 7 ml 2,3-dimethyl-2-butene was added, degassed by freeze thaw cycles and the mixture irradiated in a sealed Pyrex tube with medium pressure mercury lamp at about 10° for 110 hr. The mixture shows by GC analysis 94% conversion. Purification was performed on silica gel column with hexane/ether mixture as eluent, and 366.5 mg (76.2%) of V was isolated as a colorless oil, ^1H NMR (δ, $CDCl_3$) 6.98–7.64 (m, 9H, aromatic), 1.48 (s, 6H, $2CH_3$), 1.11 (s, 6H, $2CH_3$); IR (neat) 1620 cm^{-1} (C=N); mass spectrum *m/e* 295 (M^+, 1%), 239 (48), 223 (37), 212 (base peak).

Direct and sensitized photoreactions of 3-phenyl-1,2-benzisothiazole (Ia) *in ethyl vinyl ether.* Ia (10 mg) in ethyl vinyl ether (0.012 M) was irradiated with 366 nm light [obtained from a medium-pressure mercury lamp using Corning filters 0–52 and 7–60], in the presence and absence of 50 mg xanthone. GC analysis indicated no sensitization.

Reaction in dark. Compound Ia, (20 mg) was dissolved in 5 ml ethyl vinyl ether and refluxed for 2 days. The ether was evaporated and no benzothiazepine was detected by NMR.

Solvent effect on product formation in the photoreaction of 3-phenyl-1,2-benzisothiazole (Ia) *with ethyl vinyl ether.* Ethyl vinyl ether (0.5 ml) was added to the 0.004 M soln of Ia in ethyl vinyl ether, acetonitrile, benzene or hexane. The samples were degassed by freeze thaw cycles and irradiated in the sealed Pyrex tubes. After 1 hr irradiation 51% of IIa was obtained in ethyl vinyl ether as a solvent while the yield in acetonitrile was 16% and in benzene and hexane 11% and 13%, respectively. The rate of reaction was followed by NMR. The amount of product formation at various time is plotted (Fig. 3).

X-Ray analysis of IIa. The unit cell contains two independent molecules of I (two molecules which are not related by crystallographic symmetry). The conformations of the two independent molecules are essentially the same (compare the torsion angles in Table 3).

The crystals were monoclinic, space group $P2_1/n$, with a = 18.273(4), b = 10.565(2), c = 16.706(4) A, β = 110.82(1)°, and d_{calcd} = 1.248 g cm^{-3} for Z = 8 ($C_{17}H_{17}NOS$, M = 283.39). The intensity data were measured on a Hilger–Watts diffractometer (Ni filtered Cu Kα radiation, θ–2θ scans, pulse height discrimination). A crystal measuring approximately 0.15 × 0.18 × 0.7 mm was used for data collection; the data were corrected for absorption (λ = 18.0 cm^{-1}). A total of 4067 reflections were measured for θ 57°, of which 3667 were considered to be observed [I 2.5σ(I)]. The structure was solved by a multiple soln procedure[20] and was refined by full-matrix least squares. In the final refinement anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors were used for the H atoms. The hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final discrepancy indices are R = 0.034 and wR = 0.044 for the 3667 observed reflections. The final difference map has no peaks greater than ±0.2 e A^{-3}. Tables 1–3 summarize the various bond angles, bond lengths and some important torsional angles.

Hydrolysis of the photoproducts. 2,3 - *Dihydro* - 3 - *ethoxy* - 5 - *phenyl* - 1,4 - *benzothiazepine* (IIa) (5 mg) was treated with 5 ml 3 N HCl at room temp. After neutralization with Na_2CO_3 and extraction with ether the starting material (IIa) was recovered.

The acidic mixture of IIa (5 mg in 5 ml 3 N HCl) was heated on water bath to 50° for 15–20 min or heated to reflux. After the usual work up procedure (neutralization, extraction with ether) a product identical to the authentic VI,[21] was isolated.

Hydrochloride salt of V. Compound V (25 mg) was dissolved in CCl_4 and the HCl gas was introduced. Immediately after the introduction of HCl gas the yellow hydrochloride salt pre-

Table 1. Bond lengths (A) in with standard deviations in parentheses

	unprimed	primed
S - C(2)	1.810(2)	1.801(2)
S -C(10)	1.775(2)	1.771(2)
O(1)- C(3)	1.417(2)	1.417(2)
O(1)-C(18)	1.422(3)	1.426(3)
N(4)- C(3)	1.452(2)	1.454(2)
N(4)- C(5)	1.278(2)	1.276(3)
C(2)- C(3)	1.521(3)	1.519(3)
C(5)-C(11)	1.500(3)	1.491(3)
C(5)-C(12)	1.487(2)	1.494(2)
C(6)- C(7)	1.388(3)	1.382(4)
C(6)-C(11)	1.389(3)	1.397(3)
C(7)- C(8)	1.376(3)	1.375(3)
C(8)- C(9)	1.381(4)	1.373(4)
C(9)-C(10)	1.387(3)	1.392(3)
C(10)-C(11)	1.398(2)	1.403(3)
C(12)-C(13)	1.394(3)	1.387(3)
C(12)-C(17)	1.384(3)	1.383(3)
C(13)-C(14)	1.384(3)	1.382(3)
C(14)-C(15)	1.380(3)	1.372(4)
C(15)-C(16)	1.377(3)	1.372(4)
C(16)-C(17)	1.390(3)	1.395(3)
C(18)-C(19)	1.489(3)	1.492(3)

Table 2. Bond angles (°) in with standard deviations in parentheses

	unprimed	primed
C(2)- S -C(10)	100.9(1)	102.6(1)
C(3)- O(1)-C(18)	112.1(1)	113.4(2)
C(3)- N(4)- C(5)	118.3(2)	118.8(2)
S - C(2)- C(3)	113.1(1)	114.0(1)
O(1)- C(3)- N(4)	109.2(1)	109.1(2)
O(1)- C(3)- C(2)	105.8(2)	105.4(2)
N(4)- C(3)- C(2)	112.4(2)	113.5(2)
N(4)- C(5)-C(11)	123.4(2)	124.8(2)
N(4)- C(5)-C(12)	117.8(2)	116.9(2)
C(11)- C(5)-C(12)	118.8(2)	118.3(2)
C(7)- C(6)-C(11)	120.7(2)	121.0(2)
C(6)- C(7)- C(8)	119.6(3)	120.1(2)
C(7)- C(8)- C(9)	120.5(2)	120.2(2)
C(8)- C(9)-C(10)	120.4(2)	120.5(2)
S -C(10)- C(9)	120.1(1)	118.8(1)
S -C(10)-C(11)	120.3(2)	121.0(2)
C(9)-C(10)-C(11)	119.6(2)	120.0(2)
C(5)-C(11)- C(6)	120.4(1)	120.1(2)
C(5)-C(11)-C(10)	120.3(2)	121.7(2)
C(6)-C(11)-C(10)	119.3(2)	118.2(2)
C(5)-C(12)-C(13)	119.8(2)	119.3(2)
C(5)-C(12)-C(17)	121.4(2)	121.4(2)
C(13)-C(12)-C(17)	118.7(2)	119.2(2)
C(12)-C(13)-C(14)	120.4(2)	120.5(2)
C(13)-C(14)-C(15)	120.5(2)	120.0(2)
C(14)-C(15)-C(16)	119.5(2)	120.2(2)
C(15)-C(16)-C(17)	120.4(2)	120.1(2)
C(12)-C(17)-C(16)	120.5(2)	119.9(2)
O(1)-C(18)-C(19)	109.0(2)	108.3(2)

Table 3. Torsion angles (°) in with standard deviations in parentheses

	unprimed	primed
C(10)- S - C(2)- C(3)	-33.3(2)	-31.3(2)
S - C(2)- C(3)- N(4)	-51.6(2)	-51.3(2)
C(2)- C(3)- N(4)- C(5)	84.6(2)	84.2(2)
C(3)- N(4)- C(5)-C(11)	-1.7(3)	-4.8(3)
N(4)- C(5)-C(11)-C(10)	-51.7(3)	-47.5(3)
C(5)-C(11)-C(10)- S	-6.7(3)	-6.7(3)
C(11)-C(10)- S - C(2)	67.3(2)	64.1(2)
S - C(2)- C(3)- O(1)	-170.7(1)	-170.7(1)
C(2)- C(3)- O(1)-C(18)	-172.6(2)	-176.0(2)
C(3)- O(1)-C(18)-C(19)	173.4(2)	169.0(2)
C(3)- N(4)- C(5)-C(12)	177.1(2)	172.5(2)
N(4)- C(5)-C(12)-C(13)	-24.1(3)	-36.8(3)

cipitated in quantitative yield, m.p. 238°; ^{1}H NMR (δ, $CDCl_3$) 7.1–8.0 (m, 9, aromatic), 1.66 (s, 3, CH_3), 1.52 (s, 3, CH_3), 1.49 (s, 6H, $2CH_3$).

Hydrolysis of V. When V (5 mg) was refluxed in 5 ml 3N HCl for 3 days and the mixture worked up in the usual manner, a product was isolated which, based on spectral data, was identified as VII, IR (neat) 3370 and 3310 cm^{-1} (NH_2), 1670 cm^{-1} (C=O); ^{1}H NMR (δ, $CDCl_3$), 7.3–7.8 (m, 9, aromatic), 1.17 and 1.10 (2s, 12H, $4CH_3$), 1.41 (s, 2H, NH_2).

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